RECOMBINANT ANTI-TUMOR RNASE

CROSS REFERENCE TO RELATED APPLICATIONS

~~Not applicable.~~ see Examiner's Amendment 10.20.01

FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

Not applicable.

BACKGROUND OF THE INVENTION

Ribonucleases such as ribonuclease A ("RNase A") and their cytotoxicity towards tumor cells were discovered in the 1960s (reviewed in Roth, J., *Cancer Res.* **23**:657-666 (1963)). In the 1970s, human serum was also discovered to contain several RNAses that are expressed in a tissue specific manner (Reddi, E., *Biochem. Biophys. Res. Commun.* **67**:110-118 (1975); and Blank, *et al.*, HUMAN BODY FLUID RIBONUCLEASES: DETECTION, INTERRELATIONSHIPS AND SIGNIFICANCE, pp203-209 (IRL Press, London, 1981)).

Further to these early studies was the discovery that an anti-tumor protein from oocytes of *Rana pipiens* had homology to RNAse A (Ardelt, *et al.*, *J. Biol. Chem.* **256**:245-251(1991)). This protein was termed ONCONASE®, Alfacell Corporation, N.J. See also *e.g.*, Darzynkiewicz, *et al.*, *Cell Tissue Kinet.* **21**:169-182 (1988); Mikulski, *et al.*, *Cell Tissue Kinet.* **23**:237-246 (1990); and U.S. Patent No. 4,888,172).

Phase I and Phase I/II clinical trials of ONCONASE® as a single therapeutic agent in patients with a variety of solid tumors (Mikulski, *et al.*, *Int. J. of Oncology* **3**: 57-64 (1993)) or combined with tamoxifen in patients with advanced pancreatic carcinoma have been completed (Chun, *et al.*, *Proc. Amer. Soc. Clin. Oncol.* **14**:210 (1995)) and the protein has been found to be efficacious in pancreatic, renal cell, and prostate cancers as well as mesothelioma.

Conjugation of ONCONASE® to cell-type-specific ligands was found to increase its potency towards tumor cells (Rybak, *et al.*, *Drug Delivery* 1:3-10 (1993)).